REMARKS

Claim Status

Claims 1-33, 37 and 38 are pending in this application. Claims 1, 17 and 31 are amended herein. Support for the claim amendments is provided by the specification, at, e.g., page 1, lines 9-15, and by the language of each claim as previously presented. No new matter is added by way of these amendments. Entry of the claim amendments and reconsideration in view of the following remarks are respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-33, 37 and 38 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 98/34644 for reasons of record. Briefly, the rejection asserts that WO 98/34644 discloses the use of PDT to reduce inflammation in injured or pre-injured tissues. The rejection contends that tissues that overlap with the tissues treated with normal dose PDT are "pre-injured" tissues and, therefore it allegedly would have been obvious to treat such overlapping tissues with low dose PDT. Applicants respectfully traverse the rejections, for reasons of record as well as at least the following reasons.

The statement of rejection contradicts a previously position asserted by the Office

The rejection contends that WO 98/34644 teaches the steps of "1) bringing the injured tissues or 'pre-injured tissues' [into contact] with a photosensitizing agent capable of penetrating into the tissue and 2) exposing the tissue to the light having wave length absorbed by photosensitizing agent for a time sufficient to reduce or prevent inflammation." Office Action at page 3, first paragraph. In addition, the rejection states that: "It would have been obvious to a person skilled in the art to use low dose PDT for the treatment of inflammation, considering that the tissues overlapping with tissues subjected to photodynamic therapy are considered to be pre-injured tissues, which reads on the teachings of the above reference." Office Action at page 3, first paragraph.

The allegation that it would have been obvious to treat both "injured" and "pre-injured" tissues based on the cited document is inconsistent with the Office's previously asserted position regarding the non-enablement of claims to "preventing inflammation." In the Office Actions mailed October 30, 2006 and May 17, 2006, a rejection stated that "the prior art does not recognize that prevention of inflammation is easily accomplished" and that "preventing inflammation arising from photodynamic therapy should be determined by painstaking experimentation...." Office Action of May 17, 2006, at pages 2-3.

While Applicants do not agree with the Office's position regarding "preventing inflammation," Applicants respectfully point out that the Office's position contradicts the statement of the instant rejection. If there is no enablement for preventing inflammation as alleged, then the Office has provided no rationale as to why the skilled person would have found it obvious to treat the larger concentric circle containing adjacent tissue (which is characterized as "pre-injured") based on WO 98/34644, especially in view of the state of the art as previously alleged by the Office.

Applicants respectfully submit that the instant rejection may not be maintained because the position being asserted contradicts another position asserted by the Office.

The statement of rejection fails to address all of the features of the claimed invention

To identify the differences between the claimed invention and the cited document, the instant rejection asserts that the document "differs from the claimed invention in reducing inflammation in tissues exposed to photodynamic therapy and the tissues that overlap with the tissues that have been treated with normal dose PDT." Office Action at page 3, first paragraph. Applicants submit that these differences acknowledged by the Examiner relate to critical features of the invention as claimed and are themselves sufficient to establish the non-obviousness of the claimed invention.

Additionally, Applicants point out that the rejection has disregarded at least one other significant difference between the invention as claimed and the cited document. The additional

difference is the lack of any teaching or suggestion of exposing a tissue to low dose PDT in a concentric circle around an area previously exposed to normal dose PDT.

The Examiner asserts that "[t]he possible inflammation to the surrounding tissues exposed to photodynamic therapy is considered to be within the skill of the art." Office Action at page 5, lines 7-8. To the extent that the Office is attempting to rely on this statement to support the "concentric" feature in the claims, Applicants respectfully submit that no rationale has been provided to explain how this statement teaches or otherwise suggests the claimed feature. Additionally, no other basis or suggestion is provided for how the cited document meets the concentric circle claim feature.

Applicants respectfully submit that in the absence of an expectation of inflammation in the surrounding area, there is no motivation to treat the surrounding area unless low dose PDT is expected to prevent inflammation, which the Examiner has previously asserted is not possible.

Moreover, the Examiner's positions that overlapping or adjacent tissues constitute "pre-injured tissues" and that one of skill in the art would have been motivated to treat such tissues with low dose PDT raises an additional burden for establishing the instant rejection. The burden is that either: 1) it is known that the normal dose PDT results in inflammation in the adjacent tissue region not exposed to the normal dose PDT; or 2) it is expected or planned that treatment of the adjacent region will "prevent" inflammation that is to occur.

Regarding the first point, the Examiner states that "[t]he prior art clearly teaches that the photodynamic therapy can affect the tissues beyond the treated area, and can cause damage to such tissues as well." Office Action, page 4, lines 7-9. However, the Examiner has pointed to nothing in the cited document to support this statement. Moreover, the Examiner has certainly provided no basis to support the assertion that "[t]he prior art uses a low dose light being absorbed by a photosensitizing agent to treat inflammation caused by the normal dose photodynamic therapy." Office Action, at sentence bridging pages 4-5.

Regarding the second point, Applicants note that the assertion of the adjacent region as requiring treatment to "prevent" inflammation is inconsistent with the Examiner's previous rejection regarding "prevention of inflammation" as discussed above.

Applicants respectfully request that the Examiner provide the basis for the assertions regarding the state of the prior art as indicated above. If these assertions rely on facts within the Examiner's personal knowledge, it is respectfully requested that the Examiner clearly identify this as the basis for support and provide an affidavit to that effect to make the record complete for appeal. See, 37 CFR 1.104(d)(2).

There is no motivation to support the "obviousness" of claims 1 and 31

The obviousness rejection appears based on the assertion that WO 98/34644 reports normal dose PDT as causing inflammation and low dose PDT as being able to treat inflammation in "injured" tissue and prevent inflammation in "pre-injured" tissue. However, there is no teaching or suggestion in the cited document that as a general rule, the inflammation caused by PDT should be treated or reduced. Applicants submit that read in context, the cited document does not support the generic conclusion that reducing inflammation is desirable.

For example, WO 98/34644 at page 15 states:

> It has been recognized that the acute inflammatory phase usually induced by PDT in approved cancer treating protocols is a double-edged sword. The study of experimental tumor models has shown that, after PDT is administered, a protein- and neutral lipid-rich exudate infiltrates into the extracellular space and accumulates against a "wall" of perinecrotic vital cells ("hypoxic cells"), which are stuck against the "ghosts" of necrotic cells. From a positive cancer treatment perspective, the inflammatory exudate may help to deliver protein-bound photosensitizers to the inner areas of the tumor that would otherwise be difficult to reach. On the other hand, this flow of inflammatory exudate may also bring oxygen and nutrients and thus help to nourish cells engaged in wound repair processes. Therefore, the occurrence of an inflammatory state associated with PDT has been recognized a fact of life that often complicates the treatment of cancerous tumors. Freitas, "Inflammation and Photodynamic Therapy", *J. Photochem. and Photobiol., B: Biology, 8:* 340-41 (1991).

The Office has apparently misinterpreted the reference to inflammation as a "double-edged sword" to indicate that one of skill in the art would consider the acute inflammatory phase induced by PDT as a condition to be treated or reduced. Careful consideration of lines 18-25 in the above cited passage clearly indicates that inflammation has a "positive cancer treatment" effect by helping deliver photosensitizer to the inner areas of the tumor. The other side of the "double edged sword" is that, by bringing oxygen and nutrients, inflammation may "help nourish cells engaged in wound repair processes." There is thus no indication of negative effects. Instead, there is clearly recognition of the potential positive benefits of ensuring that the photosensitizer be distributed into "the inner areas of the tumor". Therefore, Applicants submit that a sufficient motivation has not been provided to lead one of skill in the art to believe that reducing inflammation in such treatments would be beneficial or desirable.

Further support for the Applicants' position that one of skill in the art would not be motivated to "treat" the inflammation caused by normal dose PDT is provided by Freitas (copy

attached as Exhibit A), referred to on lines 23-25 of the above cited passage. The first paragraph of Freitas on page 341 is as follows:

> From a single dose PDT viewpoint, the negative side of the inflammation which it causes may thus be tumour relapse if destruction of neoplastic cells has not been totally achieved. Several positive aspects may, however, be found for pre-existing inflammation [5], namely the exudate may help to deliver protein-bound photosensitizers to the inner areas of the tumour, its dissolved oxygen may increase the local pO_2 levels of areas distant from the vasculature with respect to the pO_2 values calculated simply in terms of oxygen diffusion and consumption, and tumour fibrin loci (obtained by clotting of extravasated fibrinogen) may provide further binding sites for the photosensitizers. If, as will probably occur, the first PDT dose is insufficient for complete eradication of the tumour, we should not discard the idea of planning the second dose in such a way as to exploit the ensuing inflammatory phase, in particular the possibility of obtaining widespread tissue distribution of the drug transported by the exudate proteins, higher cellular uptake of the drug due to the presence of a highly proliferative population, and improved oxygenation brought about by the plasma-like fluid. The negative aspects are the haemorrhage, due to the collapse of blood vessels, which will hinder light penetration in the tissue, and the possibility that two close PDT doses might not be well tolerated by the patient.

As seen from the above quote, the "negative side" of the inflammation caused by PDT treatment is the possibility of tumor relapse following single dose PDT. But rather than teaching or suggesting that it is desirable to reduce or treat the amount of PDT-induced inflammation, Freitas proposes taking advantage of the inflammation by repeating normal dose PDT treatment in treated tissue, to "exploit the ensuing inflammatory phase…." The reference to "negative aspects" in the last sentence of the quote provided above refers to the use of two normal dose PDT treatments in sequence, rather than the inflammation caused by normal dose PDT.

Assuming, *arguendo*, that one of ordinary skill in the art would believe that the use of low dose PDT as allegedly disclosed in WO 98/34644 would be suitable to reduce inflammation caused by normal dose PDT (which the Applicants do not concede), the Applicants submit that in view of Freitas, there would be no motivation to do so in the treatment of tumors. Based on the quoted portion of Freitas one of skill in the art would reasonably conclude that reduction of

inflammation by any means, including low dose PDT, would result in less effective anti-tumor therapy. Accordingly, the Applicant's submit that the alleged motivation to arrive at the claimed invention is not supported by the content of the cited document or by Freitas.

There is no motivation to support the "obviousness" of claim 17

As amended, claim 17 explicitly indicates that the normal dose PDT in step a) results in inflammation in an area adjacent to the treated area. This feature of the claims is clearly neither taught nor suggested by the cited document, which fails describe or otherwise suggest that PDT causes inflammation in an area adjacent to the PDT treated tissue area. As discussed above, the Examiner has pointed to nothing in the cited document and has provided no other basis for the assertion that treating adjacent tissue would have been obvious to one of ordinary skill at the time of the invention. Therefore, the Office has failed to establish a motivation to apply low dose PDT to an area adjacent to the treated tissue area.

There is no reasonable expectation of success

Assuming solely for the sake of argument that one of skill in the art was motivated to reduce inflammation caused by normal dose PDT in some contexts, the Applicants respectfully submit that one of skill in the art would not have had a reasonable expectation that low dose to reduce or treat inflammation caused by prior treatment with normal dose PDT would be successful to reduce or treat such inflammation.

The cited document states on page 16, lines 18-21, that "[i]n view of the well-known potentially destructive, necrotic effect of PDT in other applications, there is a need for the reduction or prevention of inflammation in such a way that the degree and extent of pharmacological activity can be reliably controlled." Thus the cited document reports the need to reduce or prevent inflammation caused by the "potentially destructive, necrotic effect of PDT" in some contexts.

Nevertheless, nowhere in the cited document is there any teaching, suggestion, or indication that low-dose PDT can be used to reduce or prevent such inflammation. Thus, in spite of the recognition of a need, the solution achieved by the instantly claimed invention was not evident to

the inventors of the cited document in 1998. This is clear evidence that the inventors named in the cited document did not expect success in using low dose PDT to reduce or treat inflammation caused by normal dose PDT. Therefore, and based on the cited document alone, there was no expectation of success in arriving at the claimed invention. In addition, the lack of any subsequent document teaching or suggesting the claimed invention is further evidence that the skilled person would not have found the invention "obvious."

In view of the foregoing remarks, Applicants submit that a *prima facie* case of obviousness has not been established. Accordingly, applicants request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

Evidence of unexpected results rebuts any *prima facie* case of obviousness, if made.

Contrary to the Examiner's assertion that the Applicants have provided no evidence of unexpected results, Applicants point out that this issue is dependent on what is considered "expected". Given that the inflammation caused by normal dose PDT is acute inflammation, the appropriate background is consideration of causes of cell injury and cell death that result in acute inflammation. Acute inflammation is the result of cell injury or cell death.

Exemplary causes of cell injury and cell death include physical agents, chemical agents, infectious diseases such as bacteria and viruses, and immunological mechanisms. The Office has provided no reasonable expectation in the field that following a first exposure to an agent that causes acute inflammation, a repeat of the exposure would result in a reduction or treatment of the inflammation. To assert that the successful treatment of inflammation by the claimed invention "is expected," the Office must provide examples, from the time of the invention, of physical or chemical agents that cause inflammation after a first exposure and are then used to reduce or treat that inflammation by a repeat of the exposure. The cited document clearly does not teach or suggest such an example.

Until there is demonstration of an expectation of repeat exposure as a means to treat or reduce inflammation, the fact that low dose PDT can be successfully used to reduce inflammation caused by normal dose PDT is an unexpected result.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 273012011800. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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